

PATENT SPECIFICATION

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(54) IMPROVEMENTS IN THE PREPARATION OF  
 16,17-CYCLIC ACETALS AND KETALS OF  
 9 $\alpha$ -HALOSTEROIDS

(71) We, LARK S.P.A., of 25/A Via F. Filzi, 20124 Milan, Italy, an Italian body corporate, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to an improved process for preparing 16,17-cyclic acetals and ketals of 9 $\alpha$ -halo-11 $\beta$ ,16 $\alpha$ ,17 $\alpha$ -trihydroxy steroids of the pregnane series.

It is known that such derivatives, particularly those with double bonds in the 1,2 and 4,5-positions, have a remarkable anti-inflammatory activity, due to the simultaneous presence, in the steroid molecule of both the acetal or ketal group in the 16,17-position and the halo-atom and hydroxy group in the 9 $\alpha$  and 11 $\beta$  positions respectively.

It is also known to those skilled in the art that the formation of the 16,17-cyclic acetal or ketal and the introduction of the 9 $\alpha$ -halo and 11 $\beta$ -hydroxy in the same steroidal molecule must be achieved by quite distinct steps, the two reactions being different and requiring specific reactants and involving different positions in the steroidal ring.

As a matter of fact, the methods described in the literature for the preparation of said derivatives consist either in treating the 16 $\alpha$ ,17 $\alpha$ -dihydroxy steroids of the pregnane series already containing the 9 $\alpha$ -halo atom and 11 $\beta$ -hydroxy group, with an aldehyde or a ketone, or by introducing such 9 $\alpha$ -halo atom and 11 $\beta$ -hydroxy group into derivatives already having the 16 $\alpha$ ,17 $\alpha$ -cyclic acetal or ketal group.

It has now surprisingly been found that by allowing the 9 $\beta$ ,11 $\beta$ -epoxides of the 16 $\alpha$ ,17 $\alpha$ -dihydroxy steroids of the pregnane series to react with a minimum quantity of an aqueous solution of hydrogen halide, not inferior obviously to that stoichiometrically required for the hydrohalogenation reaction, in the presence of the necessary quantity of the required aldehyde or ketone, it is possible to accomplish in one single step both the introduction of the halogen in the 9 $\alpha$  position and the hydroxyl group in the 11 $\beta$  position as well as the formation of the acetal or ketal groups in the 16 $\alpha$ ,17 $\alpha$  position.

According to the present invention there is provided a process for the preparation of 16 $\alpha$ ,17 $\alpha$ -cyclic acetals or ketals of 9 $\alpha$ -halo-11 $\beta$ ,16 $\alpha$ ,17 $\alpha$ -trihydroxy steroids of the pregnane series, which comprises treating the 9 $\beta$ ,11 $\beta$ -epoxides of the 16 $\alpha$ ,17 $\alpha$ -dihydroxy derivatives with a minimum quantity of aqueous hydrogen halide as long as this quantity is not below the amount stoichiometrically required for the hydrohalogenation reaction, in the presence of the necessary quantity of the selected aldehyde or ketone, and carrying out simultaneously the double reaction of hydrohalogenation and acetalization or ketalization at a temperature between -15° and +20°C without other organic diluents.

The present invention therefore enables to achieve in one single step a double operation, with evident practical and economical advantages, since the method can be used industrially. It has also been observed that the yields obtained by the improved process, which is the object of this invention, are not lower to that of the methods already known, and in some cases even higher.

A further advantage of the present invention is that the 21-esters of 21-hydroxy-9 $\alpha$ -halo-11 $\beta$ -hydroxy-16,17-cyclic acetals or ketals of the pregnane series may be obtained directly using a 21-ester starting material. These were prepared until now, according to the literature, by an additional step (consisting in the esterification of

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the primary alcohol function in 21-position) following the one of the formation of the 16,17-cyclic acetal or ketal derivatives.

According to the method of this invention, the aqueous solutions of hydrofluoric and hydrochloric acid are the preferred hydrogen halides. The concentration of hydrofluoric acid in aqueous solution is suitably comprised between 40% and 70% (w/w.) and that of hydrochloric acid between 20% and 37% (w/w.).

The quantity of hydrogen halide to be used for the conversion of 9 $\beta$ ,11 $\beta$ -epoxide into the corresponding 9 $\alpha$ -fluoro or chloro-11 $\beta$ -hydroxyderivative, according to the process of this invention, must be minimum, obviously not inferior to the quantity stoichiometrically required for the hydrohalogenation reaction, in order not to interfere with the simultaneous formation of the acetal or ketal group in the 16,17-position. This quantity may vary generally from 0.5 to 10 millilitres, and preferably from 1 to 5 millilitres per gram of the starting epoxysteroid.

Also the quantity of aldehyde or ketone necessary for the formation of the 16,17-cyclic acetal or ketal group should be comprised within certain limits and it is generally between 0.1 and 6 millilitres, preferably between 0.5 and 3 millilitres, per gram of the starting 9 $\beta$ ,11 $\beta$ -epoxy-16 $\alpha$ ,17 $\alpha$ -dihydroxysteroids.

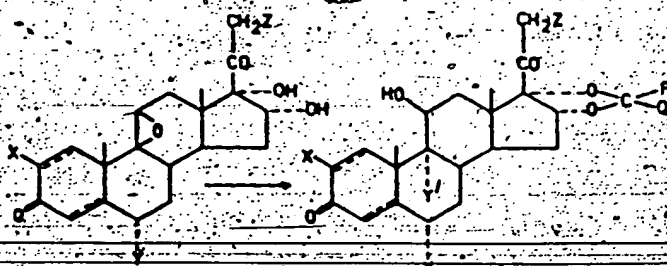
Suitable aldehydes or ketones employed according to the process of this invention are: formaldehyde (paraaldehyde), acetaldehyde, chloral hydrate, propanal, hexanal, benzaldehyde, p-chlorobenzaldehyde, p-nitrobenzaldehyde, acetone, 1-chloro-acetone, 1,2-dichloroacetone, 1,1,1-trifluoroacetone, diethylketone, dibutylketone, methyl ethylketone, methylisobutylketone, cyclopentanone, cyclohexanone, aceto-phenone, p-chloroacetophenone, p-nitroacetophenone, propiophenone, p-chloropropiophenone and benzophenone.

The above mentioned quantities of aqueous hydrogen halide and of aldehyde or ketone are the optimal ones for the complete conversion of the starting epoxide into the desired final product and for achieving higher yields during the simultaneous double reaction of hydrohalogenation and acetalization or ketalization.

As starting material for the improved process, object of this invention, any 9 $\beta$ ,11 $\beta$ -epoxy-16 $\alpha$ ,17 $\alpha$ -dihydroxy steroid of the pregnane series may be employed. Particularly suitable are the 3-keto-9 $\beta$ ,11 $\beta$ -epoxy-16 $\alpha$ ,17 $\alpha$ -dihydroxy-5 $\alpha$ -pregnanes,  $\Delta^4$ -pregnanes and  $\Delta^4$ -pregnadienes.

The presence of substituents in other positions of the steroid molecule, for example positions 2,6 and 21, does not impair the double reaction which is the characteristic feature of the process of this invention.

The method is of general application and can be particularly employed for the conversion of the 9 $\beta$ ,11 $\beta$ -epoxy-16 $\alpha$ ,17 $\alpha$ -dihydroxysteroids (Formula 1) to the corresponding 16 $\alpha$ ,17 $\alpha$ -cyclic acetals or ketals of the 9 $\alpha$ -halo-11 $\beta$ -hydroxy derivatives (Formula 2)



wherein: the dotted lines indicate the presence of a single or double bond between C<sub>1</sub> and C<sub>2</sub> and between C<sub>4</sub> and C<sub>5</sub>; when there is a single bond between C<sub>1</sub> and C<sub>2</sub>, the hydrogen in position 5 is  $\alpha$ -oriented;

X and Y are hydrogen, halogen (preferably Cl or F) or methyl; when there is a single bond between C<sub>1</sub> and C<sub>2</sub>, X is  $\alpha$ -oriented;

Y is fluorine or chlorine;

Z is hydrogen or halogen (preferably F), or a free or carboxylic acid-esterified hydroxy group;

P is hydrogen, lower (C<sub>1</sub>-C<sub>4</sub>) alkyl, halo lower (C<sub>1</sub>-C<sub>4</sub>) alkyl, cycloalkyl, benzyl, or substituted benzyl;

Q is hydrogen, lower (C<sub>1</sub>-C<sub>4</sub>) alkyl, halo lower (C<sub>1</sub>-C<sub>4</sub>) alkyl, cycloalkyl, benzyl or substituted benzyl.

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Typical examples of suitable 9 $\beta$ ,11 $\beta$ -epoxy-16 $\alpha$ ,17 $\alpha$ -dihydroxy-steroids for starting materials in the process of this invention, are:

- 9 $\beta$ ,11 $\beta$ -epoxy-16 $\alpha$ ,17 $\alpha$ -dihydroxypregn-4-ene-3,20-dione;  
 9 $\beta$ ,11 $\beta$ -epoxy-16 $\alpha$ ,17 $\alpha$ -dihydroxy-6 $\alpha$ -fluoropregn-4-ene-3,20-dione;  
 9 $\beta$ ,11 $\beta$ -epoxy-16 $\alpha$ ,17 $\alpha$ -dihydroxypregna-1,4-diene-3,20-dione;  
 9 $\beta$ ,11 $\beta$ -epoxy-16 $\alpha$ ,17 $\alpha$ -dihydroxy-21-fluoropregna-1,4-diene-3,20-dione;  
 9 $\beta$ ,11 $\beta$ -epoxy-16 $\alpha$ ,17 $\alpha$ -dihydroxy-6 $\alpha$ -methyl-21-fluoropregna-1,4-diene-3,20-dione;  
 9 $\beta$ ,11 $\beta$ -epoxy-16 $\alpha$ ,17 $\alpha$ -dihydroxy-6 $\alpha$ -chloro-21-fluoropregna-1,4-diene-3,20-dione;  
 9 $\beta$ ,11 $\beta$ -epoxy-16 $\alpha$ ,17 $\alpha$ -dihydroxy-6 $\alpha$ ,21-difluoropregna-1,4-diene-3,20-dione;  
 9 $\beta$ ,11 $\beta$ -epoxy-16 $\alpha$ ,17 $\alpha$ ,21-trihydroxy-5 $\alpha$ -pregnane-3,20-dione and corresponding 21-esters;  
 9 $\beta$ ,11 $\beta$ -epoxy-16 $\alpha$ ,17 $\alpha$ ,21-trihydroxy-6 $\alpha$ -fluoro-5 $\alpha$ -pregnane-3,20-dione and corresponding 21-esters;  
 9 $\beta$ ,11 $\beta$ -epoxy-16 $\alpha$ ,17 $\alpha$ ,21-trihydroxypregn-4-ene-3,20-dione and corresponding 21-esters;  
 9 $\beta$ ,11 $\beta$ -epoxy-16 $\alpha$ ,17 $\alpha$ ,21-trihydroxy-2 $\alpha$ -fluoropregn-4-ene-3,20-dione and corresponding 21-esters;  
 9 $\beta$ ,11 $\beta$ -epoxy-16 $\alpha$ ,17 $\alpha$ ,21-trihydroxy-2 $\alpha$ -methylpregn-4-ene-3,20-dione and corresponding 21-esters;  
 9 $\beta$ ,11 $\beta$ -epoxy-16 $\alpha$ ,17 $\alpha$ ,21-trihydroxy-6 $\alpha$ -methylpregn-4-ene-3,20-dione and corresponding 21-esters;  
 9 $\beta$ ,11 $\beta$ -epoxy-16 $\alpha$ ,17 $\alpha$ ,21-trihydroxypregna-1,4-diene-3,20-dione and corresponding 21-esters;  
 9 $\beta$ ,11 $\beta$ -epoxy-16 $\alpha$ ,17 $\alpha$ ,21-trihydroxy-2-methylpregna-1,4-diene-3,20-dione and corresponding 21-esters;  
 9 $\beta$ ,11 $\beta$ -epoxy-16 $\alpha$ ,17 $\alpha$ ,21-trihydroxy-6 $\alpha$ -chloropregna-1,4-diene-3,20-dione and corresponding 21-esters;  
 9 $\beta$ ,11 $\beta$ -epoxy-16 $\alpha$ ,17 $\alpha$ ,21-trihydroxy-6 $\alpha$ -fluoropregna-1,4-diene-3,20-dione and corresponding 21-esters;  
 9 $\beta$ ,11 $\beta$ -epoxy-16 $\alpha$ ,17 $\alpha$ ,21-trihydroxy-6 $\alpha$ -methylpregna-1,4-diene-3,20-dione and corresponding 21-esters;

Typical examples of 21-esters of the above-mentioned 9 $\beta$ ,11 $\beta$ -epoxy-16 $\alpha$ ,17 $\alpha$ ,21-trihydroxysteroids are: 21-acetates, 21-propionates, 21-butyrate, 21-valerates, 21-trimethylacetates, 21-tertbutylacetates, 21-cyclopentylpropionates and 21-benzoates.

The reaction is generally carried out as follows: the aqueous hydrogen halide employed is cooled to a temperature between 0°C and -30°C and then the selected aldehyde or ketone is added with stirring.

To this mixture the selected starting epoxysteroid is added. Alternatively and without affecting the reaction course, the steroid addition can precede the addition of the aldehyde or ketone. During the operation the reaction mixture is maintained at a temperature between -15° to +20°C.

The reaction time may vary from 2 to 24 hours, essentially depending upon the nature of the starting steroid.

The proceed of the double reaction carried out in a one single step may be controlled by thin-layer chromatography and, upon completion of the reaction, the mixture is poured in water or water containing substances able to neutralize the unreacted hydrogen halide, as, for example, alkali metal or ammonium carbonates, bicarbonates or acetates.

The resulting 9 $\alpha$ -halo-11 $\beta$ -hydroxysteroid-16 $\alpha$ ,17 $\alpha$ -cyclic acetal or ketal is isolated by filtration, washed thoroughly with water, dried and crystallized from a suitable solvent.

If the aldehyde or ketone employed is water-immiscible it is possible that no solid precipitate is formed. In this case the product may be isolated by extraction with a suitable solvent.

The following examples are given to illustrate the improved process, object of the present invention.

#### Example 1

Triamcinolone 16,17-acetonide 21-acetate

To 10 ml of 70% (w/w) aqueous solution of hydrofluoric acid previously cooled to -30°C, 5 ml of acetone are added. To this stirred solution 5 g of 9 $\beta$ ,11 $\beta$ -epoxy-16 $\alpha$ ,17 $\alpha$ ,21-trihydroxypregna-1,4-diene-3,20-dione-21-acetate are added portionwise maintaining the temperature between -20°C and -30°C. The reaction

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temperature is then allowed to rise to about  $-10^{\circ}\text{C}$  and the stirring is continued at this temperature. A thin-layer chromatography control performed after 2 hours shows the presence of about 65% of the desired product in the reaction mixture. A further control after an additional 2 hours indicates that the conversion is completed.

The reaction mixture is then slowly poured into a well stirred solution of 35.2 g of potassium carbonate in 40 ml of water, maintaining the temperature at about  $20-25^{\circ}\text{C}$ . The precipitate thus obtained is filtered, dried and crystallized from an ethyl acetate-methanol mixture to give 4.6 g of triamcinolone 16,17-acetonide 21-acetate, having the following characteristics:

M.P.  $263.5^{\circ}\text{C}$  (with decomposition)  
 $[\alpha]_{\text{D}}^{25} +94.8^{\circ}$  ( $c=1\%$ , dioxane)  
 $\lambda_{\text{max}}^{\text{KOH}} 233 \text{ m}\mu$  ( $\epsilon=16,000$ )

Following the same procedure and starting from 21-ester different from the acetate, other 21-esters of triamcinolone acetonide are prepared such as the 21-propionate, 21-butyrate, 21-valerate, 21-trimethylacetate, 21-tertbutylacetate, 21-cyclopentylpropionate and 21-benzoate.

#### Example 2

##### Triamcinolone 16,17-acetonide

To 4 ml of 70% (w/w) aqueous solution of hydrofluoric acid, previously cooled to  $-30^{\circ}\text{C}$ , 2 g of 9 $\beta$ ,11 $\beta$ -epoxy-16 $\alpha$ ,17 $\alpha$ ,21-trihydroxypregna-1,4-diene-3,20-dione are portionwise added with stirring, keeping the temperature between  $-20^{\circ}\text{C}$  and  $-30^{\circ}\text{C}$ .

To this mixture 2 ml of acetone are added and the reaction is carried out according to Example 1.

After about six hours the reaction is completed and the mixture is worked up according to Example 1. After crystallization from methanol, 1.950 g of triamcinolone acetonide of the following characteristics are obtained:

M.P.  $289^{\circ}\text{C}$  (with decomposition)  
 $[\alpha]_{\text{D}}^{25} +108.5^{\circ}$  ( $c=0.5\%$ , chloroform)  
 $\lambda_{\text{max}}^{\text{KOH}} 238 \text{ m}\mu$  ( $\epsilon=16,200$ )

#### Example 3

##### Fluocinolone 16,17-acetonide 21-acetate

Four milliliters of 70% (w/w) aqueous solution of hydrofluoric acid are treated with 2 ml of acetone as described in Example 1.

To this solution 2 g of 6 $\alpha$ -fluoro-9 $\beta$ ,11 $\beta$ -epoxy-16 $\alpha$ ,17 $\alpha$ ,21-trihydroxypregna-1,4-diene-3,20-dione 21-acetate are added portionwise maintaining the temperature between  $-20^{\circ}$  and  $-30^{\circ}\text{C}$ . The reaction is completed after about 20 hours. The reaction mixture is poured in 50 ml of a 40% aqueous solution of potassium acetate, keeping the temperature at about  $20^{\circ}\text{C}$ . The resulting precipitate is filtered, washed with water to neutral, dried, and crystallized from a chloroform-methanol mixture, giving 1.9 g of fluocinolone acetonide 21-acetate, having the following characteristics:

M.P.  $305^{\circ}\text{C}$  (with decomposition)  
 $[\alpha]_{\text{D}}^{25} +86^{\circ}$  ( $c=1\%$ , dioxane)  
 $\lambda_{\text{max}}^{\text{KOH}} 237 \text{ m}\mu$  ( $\epsilon=16,300$ )

Following the same procedure and starting from 21-esters different from the acetate, other 21-esters of fluocinolone 16,17-acetonide are prepared, such as the 21-propionate, 21-butyrate, 21-valerate, 21-trimethylacetate, 21-tertbutylacetate, 21-cyclopentylpropionate, and 21-benzoate.

#### Example 4

##### 9 $\alpha$ -Chloro-11 $\beta$ ,16 $\alpha$ ,17 $\alpha$ ,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,17-acetonide 21-acetate

Twenty milliliters of concentrate hydrochloric acid (37% w/w) are cooled to  $-20^{\circ}\text{C}$  and diluted with 2 ml of acetone. To this stirred solution 2 g of 9 $\beta$ ,11 $\beta$ -epoxy-16 $\alpha$ ,17 $\alpha$ ,21-trihydroxy-pregna-1,4-diene-3,20-dione 21-acetate are added portionwise, maintaining the temperature between  $-10^{\circ}\text{C}$  and  $-20^{\circ}\text{C}$ .

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The temperature is then allowed to rise to  $-5^{\circ}\text{C}$  and the mixture is allowed to react at this temperature for about 4 hours.

The reaction mixture is then poured cautiously into about 200 ml of a mixture of water and ice with vigorous stirring.

The resulting precipitate is filtered, washed with abundant water to neutral, dried and then crystallized from a methanol-methylene chloride mixture, yielding 2 g of the desired product, having the following characteristics:

M.P.  $246^{\circ}\text{C}$  (with decomposition)

$[\alpha]_{\text{D}}^{25} +115.8^{\circ}$  ( $c=1\%$ , dioxane)

$\lambda_{\text{max}}^{\text{N-OH}} 239-240 \text{ m}\mu$  ( $\epsilon=15,000$ )

$\nu_{\text{max}}^{\text{KBr}} 3430, 1755, 1730, 1662, 1620, 1608, 1300, 1232 \text{ and } 742 \text{ cm}^{-1}$

Following the same procedure and starting from 21-esters different from the acetate, other 21-esters of  $9\alpha$ -chloro- $11\beta,16\alpha,17\alpha,21$ -tetrahydroxypregna- $1,4$ -diene- $3,20$ -dione  $16,17$ -acetonide are prepared such as 21-propionate, 21-butyrate, 21-valerate, 21-trimethylacetate, 21-tertbutylacetate, 21-cyclopentylpropionate and 21-benzoate.

#### Example 5

##### Fluocinolone 16,17-acetonide

Two grams of  $6\alpha$ -fluoro- $9\beta,11\beta$ -epoxy- $16\alpha,17\alpha,21$ -trihydroxypregna- $1,4$ -diene- $3,20$ -dione are treated as described in Example 3. After crystallization from a chloroform-methanol mixture 1.9 g of fluocinolone acetonide are obtained showing the following characteristics:

M.P.  $268^{\circ}\text{C}$  (with decomposition)

$[\alpha]_{\text{D}}^{25} +93.5^{\circ}$  ( $c=1\%$ , dioxane)

$\lambda_{\text{max}}^{\text{N-OH}} 239 \text{ m}\mu$  ( $\epsilon=16,200$ )

#### Example 6

##### Triamcinolone 16,17-*p*-nitroacetophenide

Two milliliters of a 50% (w/w) aqueous solution of hydrofluoric acid are cooled to  $-30^{\circ}\text{C}$ . To this stirred solution first 1 g of *p*-nitroacetophenone and then, portionwise, while maintaining the temperature between  $-20^{\circ}$  and  $-30^{\circ}\text{C}$ , 1 g of  $9\beta,11\beta$ -epoxy- $16\alpha,17\alpha,21$ -trihydroxypregna- $1,4$ -diene- $3,20$ -dione are added. The reaction is carried out as described in Example 1.

At the end of the reaction (about 5 hours) the reaction mixture is poured slowly into 20 ml of a 40% aqueous solution of potassium acetate under stirring maintaining the temperature at about  $20^{\circ}\text{C}$ . The resulting crystalline products is filtered, washed with water and dried. After crystallization from ethyl acetate 1.2 g of the desired product are obtained, showing the following characteristics:

M.P.  $255^{\circ}\text{C}$  (with decomposition)

$[\alpha]_{\text{D}}^{25} +5^{\circ}$  ( $c=1\%$ , dioxane)

$\lambda_{\text{max}}^{\text{N-OH}} 245 \text{ m}\mu$  ( $\epsilon=20,200$ )

$\nu_{\text{max}}^{\text{KBr}} 3430, 1720, 1666, 1621, 1609, 1524, 1494, 1353, 1296, 1102, 1064, 972 \text{ and } 830 \text{ cm}^{-1}$

#### Example 7

##### Benzaldehyde derivative of triamcinolone 21-acetate

To 2 ml of a 50% (w/w) aqueous solution of hydrofluoric acid, previously cooled to  $-30^{\circ}\text{C}$ , first 1 ml of benzaldehyde and then 1 g of  $9\beta,11\beta$ -epoxy- $16\alpha,17\alpha,21$ -trihydroxypregna- $1,4$ -diene- $3,20$ -dione 21-acetate are portionwise added with stirring.

The reaction is carried out as described in Example 1. At the end of the reaction (about 4 hours) the reaction mixture is treated as described in Example 6. An oily product is separated, which is extracted with ethyl acetate. The combined extracts are washed with water, dried over anhydrous sodium sulfate, and concentrated. The residue obtained is taken up with methanol to give, after filtration, 1 g of a crystalline product, having the following characteristics:

M.P.  $287^{\circ}\text{C}$  (with decomposition)

$[\alpha]_{\text{D}}^{25} +57^{\circ}$  ( $c=0.5\%$ , chloroform)

$\lambda_{\text{max}}^{\text{N-OH}} 239-240 \text{ m}\mu$  ( $\epsilon=15,000$ )

$\nu_{\text{max}}^{\text{KBr}} 3430, 1764, 1730, 1666, 1614, 1607, 1300, 1238, 1088, 971 \text{ and } 831 \text{ cm}^{-1}$

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Example 8

16 $\alpha$ ,17 $\alpha$ -(4'-methyl-2'-pentylidene)triamcinolone  
Following the procedure of Example 6 but employing methylisobutylketone instead of p-nitroacetophenone, 0.950 g of the desired product are obtained, showing the following characteristics:

M.P. 245°C (with decomposition)

$[\alpha]_D^{25} +76^\circ$  (c=0.5%, chloroform)

$\lambda_{max}^{H_2O}$  239 m $\mu$  (c=15,400)

$\nu_{max}^{KBr}$  3420, 1768, 1731, 1667, 1621, 1610, 1301, 1236, 1108, 1080, 973 and 830 cm $^{-1}$ .

Example 9

9 $\alpha$ -Fluoro-16 $\alpha$ -hydroxyhydrocortisone 16,17-acetonide

Two grams of 9 $\beta$ ,11 $\beta$ - epoxy - 16 $\alpha$ ,17 $\alpha$ ,21 - trihydroxypregn - 4 - ene - 3,20 - dione are treated according to Example 1.

After 2 hours the conversion is completed and the reaction mixture is worked up as described in Example 3, to give, after crystallization from methanol-methylene chloride, 1.9 g of the desired product having the following characteristics:

M.P. 265°C (with decomposition)

$[\alpha]_D^{25} +133.4^\circ$  (c=1%, dioxane)

$\lambda_{max}^{H_2O}$  238-239 m $\mu$  (c=16,800)

Example 10

9 $\alpha$ -Fluoro-21-chloro-11 $\beta$ ,16 $\alpha$ ,17 $\alpha$ -trihydroxypregn-4-ene-3,20-dione 16,17-acetonide

One gram of 9 $\beta$ ,11 $\beta$  - epoxy - 21 - chloro - 16 $\alpha$ ,17 $\alpha$  - dihydroxypregn - 4 - ene - 3,20 - dione is treated according to Example 2. The reaction is completed within about three hours.

The mixture is worked up according to Example 1 to give, after crystallization from acetone-n hexane, 0.850 g. of the desired product, showing the following characteristics:

M.P. 255°C (with decomposition)

$[\alpha]_D^{25} +154.5^\circ$  (c=0.5%, chloroform)

$\lambda_{max}^{H_2O}$  238 m $\mu$  (c=16,300)

WHAT WE CLAIM IS:—

1. A process for the preparation of 16 $\alpha$ ,17 $\alpha$ -cyclic acetals or ketals of 9 $\alpha$ -halo-11 $\beta$ ,16 $\alpha$ ,17 $\alpha$ -trihydroxy steroids of the pregnane series, which comprises treating the 9 $\beta$ ,11 $\beta$ -epoxides of the 16 $\alpha$ ,17 $\alpha$ -dihydroxy derivatives with a minimum quantity of aqueous hydrogen halide as long as this quantity is not below the amount stoichiometrically required for the hydrohalogenation reaction, in the presence of the necessary quantity of the selected aldehyde or ketone, and carrying out, simultaneously the double reaction of hydrohalogenation and acetalization or ketalization at a temperature between -15° and +20°C without other organic diluents.

2. A process as claimed in claim 1, in which the hydrogen halide used is aqueous hydrofluoric acid in concentrations ranging from 40% to 70% (w/w).

3. A process as claimed in claim 1, in which the hydrogen halide used is aqueous hydrochloric acid in concentrations ranging from 20% to 37% (w/w).

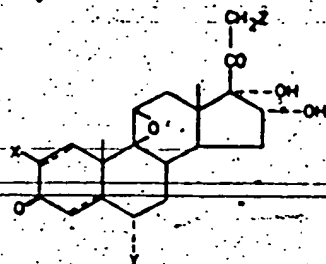
4. A process as claimed in claim 1, 2 or 3, in which the quantity of the hydrogen halide used is 0.5 to 10 millilitres per 1 gram of the starting 9 $\beta$ ,11 $\beta$ -epoxy 16 $\alpha$ ,17 $\alpha$ -dihydroxy steroid.

5. A process as claimed in any preceding claim in which the quantity of aldehyde or of ketone used is 0.1 to 6 millilitres per 1 gram of the starting 9 $\beta$ ,11 $\beta$ -epoxy 16 $\alpha$ ,17 $\alpha$ -dihydroxy steroid.

6. A process as claimed in any preceding claim, which comprises using as starting materials the 9 $\beta$ ,11 $\beta$ -epoxy-16 $\alpha$ ,17 $\alpha$ -dihydroxy derivatives of the following formula:



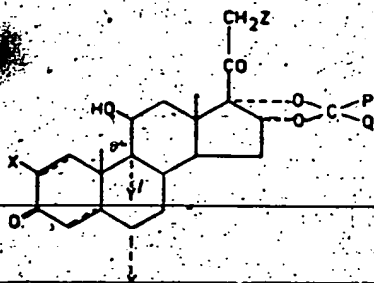
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wherein the dotted lines indicate the presence of a single or double bond between C<sub>5</sub> and C<sub>6</sub> and between C<sub>13</sub> and C<sub>14</sub>; when there is a single bond between C<sub>5</sub> and C<sub>6</sub>, the hydrogen in position 5 is  $\alpha$ -oriented;

X and Y are hydrogen or halogen or methyl; when there is a single bond between C<sub>1</sub> and C<sub>2</sub>, X is  $\alpha$ -oriented;

Z is hydrogen or halogen, or a free or carboxylic acid-esterified hydroxy group, and obtaining as end products the 9 $\alpha$ -halo-11 $\beta$ -hydroxy-16 $\alpha$ ,17 $\alpha$ -cyclic acetal or ketal derivatives corresponding to the following formula:



wherein the dotted lines X, Y and Z are as hereinbefore defined;

Y' is halogen;

P is hydrogen, lower (C<sub>1</sub>-C<sub>4</sub>) alkyl, halo lower (C<sub>1</sub>-C<sub>4</sub>) alkyl, cycloalkyl, benzyl or substituted benzyl; and

Q is hydrogen, lower (C<sub>1</sub>-C<sub>4</sub>) alkyl, halo lower (C<sub>1</sub>-C<sub>4</sub>) alkyl, cycloalkyl, benzyl or substituted benzyl.

7. A process as claimed in claim 6, in which X and Y are chlorine or fluorine, and Z is fluorine.

8. A process as claimed in claim 1 for the preparation of triamcinolone 16,17-acetonide, which comprises reacting 9 $\beta$ ,11 $\beta$ -epoxy-16 $\alpha$ ,17 $\alpha$ ,21-trihydroxy-pregna-1,4-diene-3,20-dione with aqueous hydrofluoric acid at a concentration between 40% and 70% by weight in the presence of acetone at a temperature of about -10°C.

9. A process as claimed in claim 1 for the preparation of fluocinolone 16,17-acetonide which comprises reacting 9 $\beta$ ,11 $\beta$ -epoxy-16 $\alpha$ ,17 $\alpha$ ,21-trihydroxy-6 $\alpha$ -fluoropregna-1,4-diene-3,20-dione with aqueous hydrofluoric acid at a concentration between 40% and 70% by weight in the presence of acetone at a temperature of about -10°C.

10. A process as claimed in claim 1 for the preparation of fluocinolone 16,17-acetonide 21-acetate which comprises reacting 9 $\beta$ ,11 $\beta$ -epoxy-16 $\alpha$ ,17 $\alpha$ ,21-trihydroxy-6 $\alpha$ -fluoro-pregna-1,4-diene-3,20-dione 21-acetate with aqueous hydrofluoric acid at a concentration between 40% and 70% by weight in the presence of acetone at a temperature of about -10°C.

11. A process as claimed in claim 1 for the preparation of 9 $\alpha$ -fluoro-21-chloro-11 $\beta$ ,16 $\alpha$ ,17 $\alpha$ -trihydroxypregn-4-ene-3,20-dione 16,17-acetonide which comprises reacting 9 $\beta$ ,11 $\beta$ -epoxy-21-chloro-16 $\alpha$ ,17 $\alpha$ -dihydroxypregn-4-ene-3,20-dione with aqueous hydrofluoric acid at a concentration between 40% and 70% by weight in the presence of acetone at a temperature of about -10°C.

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12. A process for the preparation of 16 $\alpha$ ,17 $\alpha$ -cyclic acetals or ketals of 9 $\alpha$ -halo-11 $\beta$ -hydroxy steroids of the pregnane series as claimed in any one of claims 1 to 10, substantially as hereinbefore described.

13. A 16 $\alpha$ ,17 $\alpha$ -cyclic acetal or ketal of a 9 $\alpha$ -halo-11 $\beta$ -hydroxy steroid of the pregnane series whenever prepared by a process as claimed in any preceding claim.

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